

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 83306534.5

(51) Int. Cl.³: **C 07 C 57/58**
C 07 C 51/487, C 07 B 19/00

(22) Date of filing: 27.10.83

(30) Priority: 29.10.82 JP 191142/82

(43) Date of publication of application:
09.05.84 Bulletin 84/19

(84) Designated Contracting States:
DE FR GB IT NL

(71) Applicant: **SUMITOMO CHEMICAL COMPANY, LIMITED**
15 Kitahama 5-chome Higashi-ku
Osaka-shi Osaka-fu(JP)

(72) Inventor: **Takuma, Kenzi**
6-3, Nishimami-2-chome Kashibacho
Kitakatsuragi-Gun Nara-ken(JP)

(72) Inventor: **Morino, Haruki**
12-12, Yanagisawa-5-chome
Hoya-shi(JP)

(74) Representative: **Paget, Hugh Charles Edward et al,**
MEWBURN ELLIS & CO. 2/3 Cursitor Street
London EC4A 1BQ(GB)

(54) **A method for optical resolution of alpha-isopropyl-p-chlorophenylacetic acid.**

(57) A method for optical resolution of α -isopropyl-p-chlorophenylacetic acid comprises reacting the α -isopropyl-p-chlorophenylacetic acid with (+)- or (-)- α -phenyl- β -(p-tolyl)ethylamine of not less than 95% in optical purity to selectively crystallize the (+)- α -phenyl- β -(p-tolyl)ethylamine salt of (+)- α -isopropyl-p-chlorophenylacetic acid or the (-)- α -phenyl- β -(p-tolyl)ethylamine salt of (-)- α -isopropyl-p-chlorophenylacetic acid, and then collecting and decomposing the resulting salt to obtain (+)- or (-)- α -isopropyl-p-chlorophenylacetic acid.

The α -isopropyl-p-chlorophenylacetic acid is useful as a carboxylic acid moiety of, for example, pyrethroid type insecticidal esters such as fenvalerate.

A METHOD FOR OPTICAL RESOLUTION OF
 α -ISOPROPYL-p-CHLOROPHENYLACETIC ACID

1 The present invention relates to a method
for optical resolution of α -isopropyl-p-chloro-
phenylacetic acid (hereinafter referred to as
ICPA). More particularly, it relates to a method
5 for the optical resolution of ICPA by using an
optically active α -phenyl- β -(p-tolyl)ethylamine
(hereinafter referred to as PTE) as an optical
resolving agent.

ICPA, an object of the present invention,
10 is the carboxylic acid moiety of, for example,
pyrethroid type insecticidal esters such as
fenvalerate. The followings are well known on said
ICPA: Its (-)-isomer has little insecticidal activity
as the ester, while the ester of its (+)-isomer
15 has an insecticidal activity of about two times
that of the (\pm)-isomer [Japanese Patent Application
Kokai (Laid-open) No. 136245/1980]. There is a
strong demand, therefore, for the development of a
method to obtain said (+)-isomer of ICPA more
20 advantageously in industry.

It is hitherto known that an optically
active PTE or α -phenethylamine is used as an optical
resolving agent for ICPA [Japanese Patent Application
Kokai (Laid-open) No. 25544/1975]. In order to
25 obtain pure (+)-ICPA of high optical purity, however,

1 it is necessary to use large quantities of solvent
and to repeat recrystallization several times; and
when (+)-PTE of low optical purity is used, the
filterability of the salt crystal becomes extremely
5 poor, thereby making it difficult to obtain (+)-ICPA
of high optical purity. It may therefore be said
that, in order to obtain (+)-ICPA of high optical
purity, this method is still not always satisfactory
in that it is obliged to use (+)-PTE of high optical
10 purity. Also, as an improved method to solve the
foregoing problems, it is known that, by using
a mixed solvent comprising hydrophobic and
hydrophilic organic solvents and/or water as a
solvent for resolution, the optical purity of
15 (+)-ICPA obtained improves, the amount of solvent
used can be decreased, and besides that, if (+)-PTE
used is of low optical purity, there is not a
lowering in the filterability of the salt crystal
[Japanese Patent Application Kokai (Laid-open)
20 No. 136245/1980].

In the course of a further study on a
method for the optical resolution of ICPA, the present
inventors found that, in the combination of ICPA and
PTE, a complex salt is formed at a 1:1:1:1 molar
25 ratio of (+)-ICPA : (-)-ICPA : (+)-PTE : (-)-PTE,
said salt is easy to deposit as crystal because of
its low solubility, and that the presence of said
salt makes the filterability of the salt crystal

1 markedly poor in the operation of optical resolution.

 This means that: In the resolution of
 (±)-ICPA, the use of (+)-PTE of low optical purity
 produces the above complex salt corresponding to
5 the amount of coexisting (-)-PTE, and because of
 said salt being lower in solubility than the (+)-ICPA-
 (+)-PTE salt and easy to deposit as crystal, it
 results that when the crystal portion is collected
 by filtration and decomposed, ICPA of lowered optical
10 purity is obtained; and for the same reason, it is
 also difficult to obtain ICPA in high purity and
 high yield by recrystallization.

 As a result of an extensive study based on
 this novel fact, the present inventors found that,
15 by carrying out the optical resolution of ICPA with
 (+)-PTE of 95% or more in optical purity, (+)-ICPA
 of high optical purity can be obtained in high yield
 without special purification and also with a good
 filterability of the crystal. The present inventors
20 thus attained to the present invention.

 Next, the method of the present invention
 will be illustrated in detail. ICPA and PTE each
 has one asymmetric carbon atom in the molecule,
 and there are four optical isomers for the salt.
25 Hereinafter, four said optical isomers are abbreviated
 as follows:

(+)-ICPA-(+)-PTE salt	(+)(+)
(-)-ICPA-(+)-PTE salt	(-)(+)
(+)-ICPA-(-)-PTE salt	(+)(-)
(-)-ICPA-(-)-PTE salt	(-)(-)

1 Of four these isomers, (+)(+) and (-)(-) are enantiomeric to each other, and the same applies also to (-)(+) and (+)(-). When a mixture of the same amounts of (+)(+) and (-)(-) is recrystallized, 5 a racemic compound is produced, and similarly, the same amounts of (-)(+) and (+)(-) also produce the same racemic compound. From the powder X-ray diffraction patterns in Figs. 2 to 5 shown later and infrared absorption spectra, this compound turned 10 out to be a complex salt comprising (+)-ICPA, (-)-ICPA, (+)-PTE and (-)-PTE, different compounds from the materials described above, in a molar ratio of 1:1:1:1 [hereinafter, said complex salt is abbreviated as (±)(±)]. From other combinations of 15 two isomers than those described above, that is, from those of (+)(+) and (-)(+), (-)(-) and (+)(-), (+)(+) and (+)(-) and (-)(-) and (-)(+), the formation of complex salt is not found. As shown in Fig. 1, with respect to the solubility of said complex salt, 20 (±)(±) has the smallest solubility in, for example, a 90% methanol solvent (containing 10% of water),

- 5 -

and (-) (+) has the largest solubility in such solvent, which is much different from those of (+) (+) and (+) (+). This tendency is also the same with other solvents.

5 We find therefore that, provided that the optical purity of the (+)-PTE or (-)-PTE is sufficiently high to avoid significant formation of the abovementioned enantiomeric isomers of ICPA-PTE (and so prevent crystallization of the abovementioned racemic 1:1:1:1
10 complex compounds), then a (+)-ICPA-(+)-PTE or (-)-ICPA-(-)-PTE salt of high optical purity can be obtained. Thus, where the purity of the (+)-PTE or (-)-PTE is at least 95%, then the corresponding optically active salt can be obtained in high purity. There is
15 thus no need for repeated purification of the optically active PTE before it is employed in an optical resolution method of the present invention.

Typically the optically active PTE may have an optical purity within the range 95-98.5%.

Next, the operating condition of the present invention will be illustrated with reference to a method to obtain (+)-ICPA using (+)-PTE.

First, ICPA is reacted with (+)-PTE to
5 form a salt. As to the optical purity of (+)-PTE used here, the higher, the more preferred. Repetition of purification, which is not always advantageous in industry, is necessary to obtain a substantially pure (+)-PTE, however, and (+)-PTE having an optical
10 purity of not less than 95%, preferably not less than 97%, can be used.

The amount of (+)-PTE is in a range of 0.5 to 1.0 mole, more preferably 0.6 to 0.8 mole, based on 1 mole of ICPA.

15 A temperature at which said reaction is carried out is optional, but for raising the optical purity of (+)-ICPA to a higher level, it is preferred to once heat to 40°C to 150°C and maintain the temperature on or after the reaction.

20 On said reaction, the use of inert solvent is preferred in carrying out the reaction smoothly, but it is not always necessary for the solvent to be the same as that used on crystallization and separation described later.

1 On said reaction, if the heating and
temperature maintenance are once carried out, it is
not always necessary for the salt to be in complete
solution.

5 Next, the ICPA-PTE salt thus formed is
crystallized in the solvent. In this case, it is
preferred that the solution is cooled slowly.

 As the solvent used on this crystallization,
there may be given for example lower alcohols such
10 as methyl alcohol, ethyl alcohol, n-propyl alcohol,
isopropyl alcohol, n-butyl alcohol, isobutyl alcohol,
sec-butyl alcohol, tert-butyl alcohol, etc., and
lower aliphatic ketones such as acetone, methyl ethyl
ketone, etc. These solvents may be used in a mixture
15 with water. Further, these alcohols, ketones and
their mixtures with water may be used in mixtures
with aromatic hydrocarbons (e.g. benzene, toluene,
xylene), aliphatic ones (e.g. hexane, heptane,
octane), alicyclic ones (e.g. cyclohexane, methyl-
20 cyclohexane) or halogenated ones (e.g. chloroform,
carbon tetrachloride, chlorobenzene). The amount of
the solvent is preferably 1 to 15 times by weight.

 A temperature at which this crystallization
is carried out is 0°C to 60°C, more preferably 10°C
25 to 30°C.

 Next, the crystallized salt crystal is
separated from the mother liquor by means such as
filtration, decantation and the like.

1 The crystal of salt thus obtained
may be directly used as a material of the pro-
duction of the (+)-ICPA ester, but it is preferred
to decompose the salt into (+)-ICPA or its alkali
5 salt by the usual method with an acid (e.g. hydro-
chloric acid; sulfuric acid) or an alkali (e.g.
sodium hydroxide, potassium hydroxide), and then to
convert the (+)-ICPA or alkali salt to the ester of
(+)-ICPA.

10 The (+)-ICPA obtained by the method above,
even by itself, has a sufficiently high optical
purity, but if necessary, its optical purity may be
heightened by recrystallization on the stage of the
salt or after decomposition of the salt into (+)-
15 ICPA.

When (-)-ICPA of high optical purity is
required, this object can be attained, as a matter
of course, by carrying out completely the same
operation using (-)-PTE of not less than 95% in
20 optical purity.

Next, the present invention will be
illustrated in more detail with reference to the
following examples.

The (+)/(-) ratio of ICPA and PTE in the
25 examples was obtained as follows: After decomposing
the ICPA-PTE salt as usual, said ratio of ICPA
was measured by the method described in M. Horiba
et al., Agric. Biol. Chem., 43, 2311 (1979) and

- 1 that of PTE by the method described in M. Horiba et al.,
Agric. Biol. Chem., 44, 2987 (1980).

Example 1

- 191.40 Grams of 90% methanol (containing
5 10% of water) was added to 63.80 g of ICPA, and
ICPA was dissolved with stirring. Thereafter, 41.21 g
of (+)-PTE (optical purity, 98.4%) was added, and
the mixture was refluxed with heating. After 2 hours'
refluxing, the reaction solution was cooled at
10 a rate of about 1°C/5 minutes, and after the temper-
ature reached 20°C, the solution was kept at the
same temperature for 1 hour. The deposited crystal
was collected by filtration, washed with a suitable
amount of 90% methanol and dried to obtain a (+)-ICPA-
15 (+)-PTE salt of the following composition.

- At the same time, a comparative experiment
was carried out in the same manner as above except
t at (+)-PTE of 91.6% in optical purity was used
in place of the (+)-PTE of 98.4% in optical purity.
20 The (+)-ICPA-(+)-PTE salt thus obtained was compared
with that obtained above.

Result

Optical purity of (+)-PTE used		[Method of the present invention]	[Comparative experiment]
		98.4%	91.6%
(+) -ICPA- (+) -PTE salt obtain- ed	Yield (amount)	47.32 g	49.86 g
	Yield (%) [*]	74.4%	78.2%
	ICPA (+)/(-) (Optical purity)	97.4/2.6 (94.8%)	90.4/9.6 (80.8%)
	PTE (+)/(-) (Optical purity)	100.0/0.0 (100.0%)	95.2/4.8 (90.4%)

*Based on (+)-ICPA contained.

- 1 60.00 Grams of 90% methanol was added to
30.00 g of the (+)-ICPA-(+)-PTE salt obtained in
the comparative experiment, and the mixture was
refluxed with heating. After 2 hours' refluxing,
5 the reaction solution was cooled to 20°C in 2 hours
and kept at the same temperature for 1 hour. There-
after, the crystal was collected by filtration,
washed with a suitable amount of 90% methanol and
dried to obtain 26.37 g of a (+)-ICPA-(+)-PTE salt.
- 10 Yield: 87.9% (based on the salt fed)
ICPA (+)/(-) = 95.0/5.0
Optical purity of (+)-ICPA is therefore 90.0%.
PTE (+)/(-) = 96.8/3.2

1 Optical purity of (+)-PTE is therefore 93.6%.

 As the above experiment shows, when (+)-PTE
of low optical purity was used, a remarkable improve-
ment in the optical purity of both (+)-ICPA and
5 (+)-PTE is not observed even by recrystallization.

Example 2

 21.27 Grams of ICPA was dissolved in
230.27 g of 90% methanol (containing 10% of water)
with stirring, and after adding 21.13 g of (+)-PTE
10 (optical purity, 100%) at 50°C, the mixture was
refluxed with heating. After 2 hours' refluxing,
the reaction solution was cooled at a rate of about
1°C/5 minutes, and one spatulaful of a (+)-ICPA-(+)-PTE
salt was added as seed crystal at 60°C during
15 cooling. After the temperature reached 20°C, the
reaction solution was kept at the same temperature
for 1 hour. The deposited crystal was collected by
filtration, washed with a suitable amount of 90%
methanol and dried to obtain 17.33 g of a (+)-ICPA-
20 (+)-PTE salt.

Yield: 81.8% [based on (+)-ICPA contained]

ICPA (+)/(-) = 97.7/2.3

Optical purity of (+)-ICPA is therefore 95.4%.

PTE (+)/(-) = 100.0/0.0

1 Example 3

A mixed solvent comprising 34.02 g of methanol, 8.51 g of water and 87.07 g of toluene was added to 63.80 g of ICPA, and the ICPA was dissolved
5 with stirring. Thereafter, 41.21 g of (+)-PTE (optical purity, 95.4%) was added at 50°C, and the mixture was refluxed with heating. The subsequent procedure was carried out in the same manner as in Example 1 except that 80% methanol (containing 20% of
10 water) was used for washing the crystal after filtration. Thus, 42.91 g of (+)-ICPA-(+)-PTE salt was obtained.

Yield: 67.4% [based on (+)-ICPA contained]

ICPA (+)/(-) = 98.2/1.8

15 Optical purity of (+)-ICPA is therefore 96.4%.

PTE (+)/(-) = 100.0/0.0

Example 4

63.80 Grams of ICPA was dissolved in a mixed solvent comprising 114.84 g of ethanol, 12.76 g
20 of water and 127.60 g of toluene, and after adding 41.21 g of (+)-PTE (optical purity, 97.2%), the mixture was refluxed with heating. The subsequent procedure was carried out in the same manner as in Example 1 except that 90% ethanol (containing 10%
25 of water) was used for washing the crystal after filtration. Thus, 44.51 g of a (+)-ICPA-(+)-PTE salt was obtained.

- 1 Yield: 70.0% [based on (+)-ICPA contained]
ICPA (+)/(-) = 97.2/2.8
Optical purity of (+)-ICPA is therefore 94.4%.
PTE (+)/(-) = 100.0/0.0

5 Brief Explanation of the Drawing:

Fig. 1 shows the solubility of a complex salt comprising (+)-ICPA, (-)-ICPA, (+)-PTE and (-)-PTE in a molar ratio of 1:1:1:1, a (+)-ICPA-(+)-PTE salt and a (-)-ICPA-(+)-PTE salt in a 90% methanol
10 solvent (containing 10% of water). The curves (1), (2) and (3) correspond to the above salts, respectively. In the figure, the ordinate indicates the solubility (wt.%), and the abscissa a temperature (°C).

Figs. 2 to 5 show the powder X-ray diffraction
15 pattern of a mixture comprising the same amounts of a (+)-ICPA-(+)-PTE salt and a (-)-ICPA-(-)-PTE salt, a crystal obtained by recrystallization of said mixture, a mixture comprising the same amounts of a (-)-ICPA-(+)-PTE salt and a (+)-ICPA-(-)-PTE salt
20 and a crystal obtained by recrystallization of said mixture. In the figure, the ordinate indicates a relative strength and the abscissa 2θ (θ , diffraction angle).

CLAIMS:

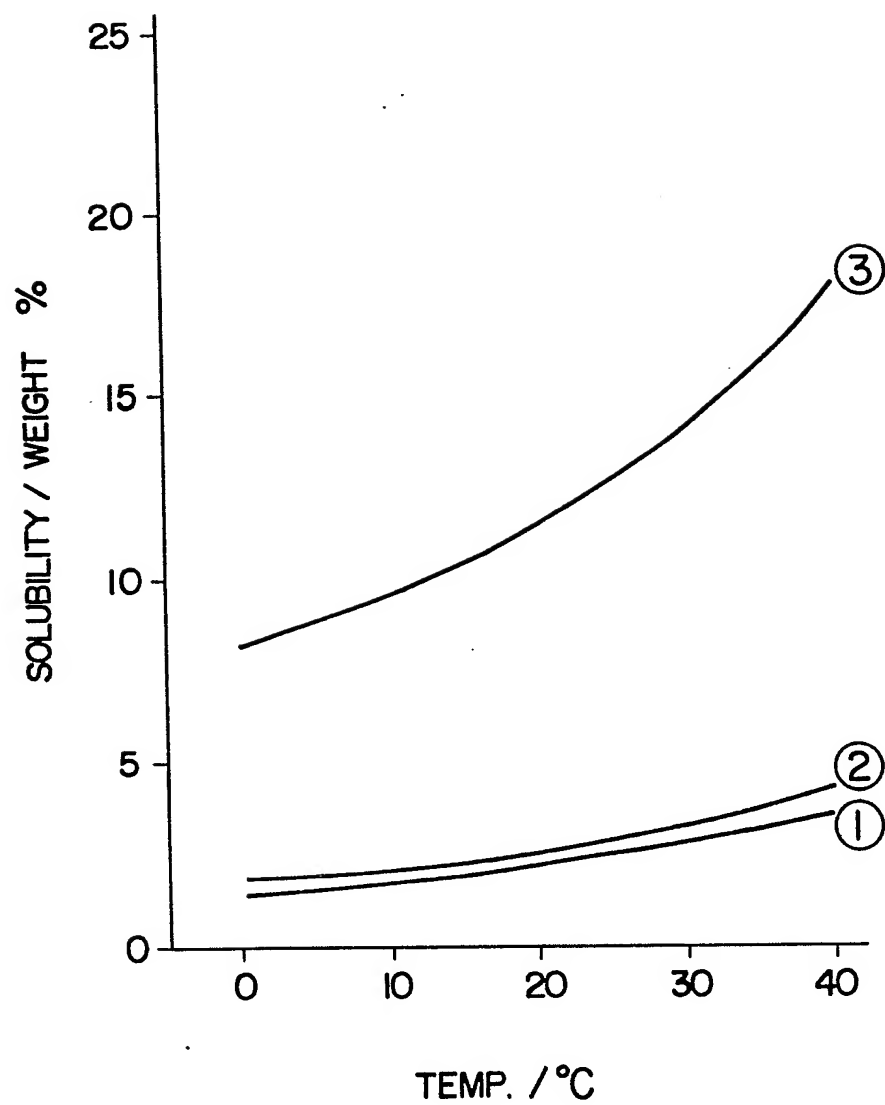
1. A method for optical resolution of α -
isopropyl-p-chlorophenylacetic acid/which comprises
(ICPA)
reacting the α -isopropyl-p-chlorophenylacetic acid
with (+)- or (-)- α -phenyl- β -(p-tolyl)ethylamine (PTE) of
5 not less than 95% in optical purity to selectively
crystallize the (+)- α -phenyl- β -(p-tolyl)ethylamine
salt of (+)- α -isopropyl-p-chlorophenylacetic acid or
the (-)- α -phenyl- β -(p-tolyl)ethylamine salt of
(-)- α -isopropyl-p-chlorophenylacetic acid, and then
10 collecting and decomposing the resulting salt to
obtain (+)- or (-)- α -isopropyl-p-chlorophenylacetic
acid.
2. A method according to claim 1, wherein the
(+)-PTE isomer is employed to yield (+)-ICPA.
- 15 3. A method according to claim 1 or claim 2,
wherein the optical purity of the (+)- or (-)-PTE is
at least 97%.
4. A method according to claim 1 or claim 2,
wherein the optical purity of the (+)- or (-)-PTE is
20 from 95-98.5%.
5. A method according to any one of the preceding
claims, wherein the solvent is a polar solvent or a
mixture thereof with a hydrophobic solvent.
6. A method of preparing an optically active
25 isomer of ICPA, which method comprises reacting a
racemic ICPA with (+)- or (-)-PTE having an optical
purity of not less than 95%, allowing the resultant
respective (+)-ICPA-(+)-PTE or (-)-ICPA-(-)-PTE salt
to crystallize, and either directly trans-esterifying
30 the resultant salt or decomposing the said salt into
(+)-ICPA or (-)-ICPA respectively, or an alkali salt
thereof and then esterifying the resultant said ICPA
or alkali salt thereof.

- 15 -

7. A method for optical resolution of racemic
ICPA which comprises reacting the racemic ICPA with
(+)- or (-)-PTE to yield (+)-ICPA-(+)-PTE or (-)-ICPA-
(-)-PTE salt respectively, allowing the said salt to
5 crystallize and then collecting and decomposing the
said salt to obtain (+)- or (-)-ICPA, characterized in
that the optical purity of the (+)- or (-)-PTE is not
less than 95%.

1/5

FIG. 1



2/5

FIG. 2

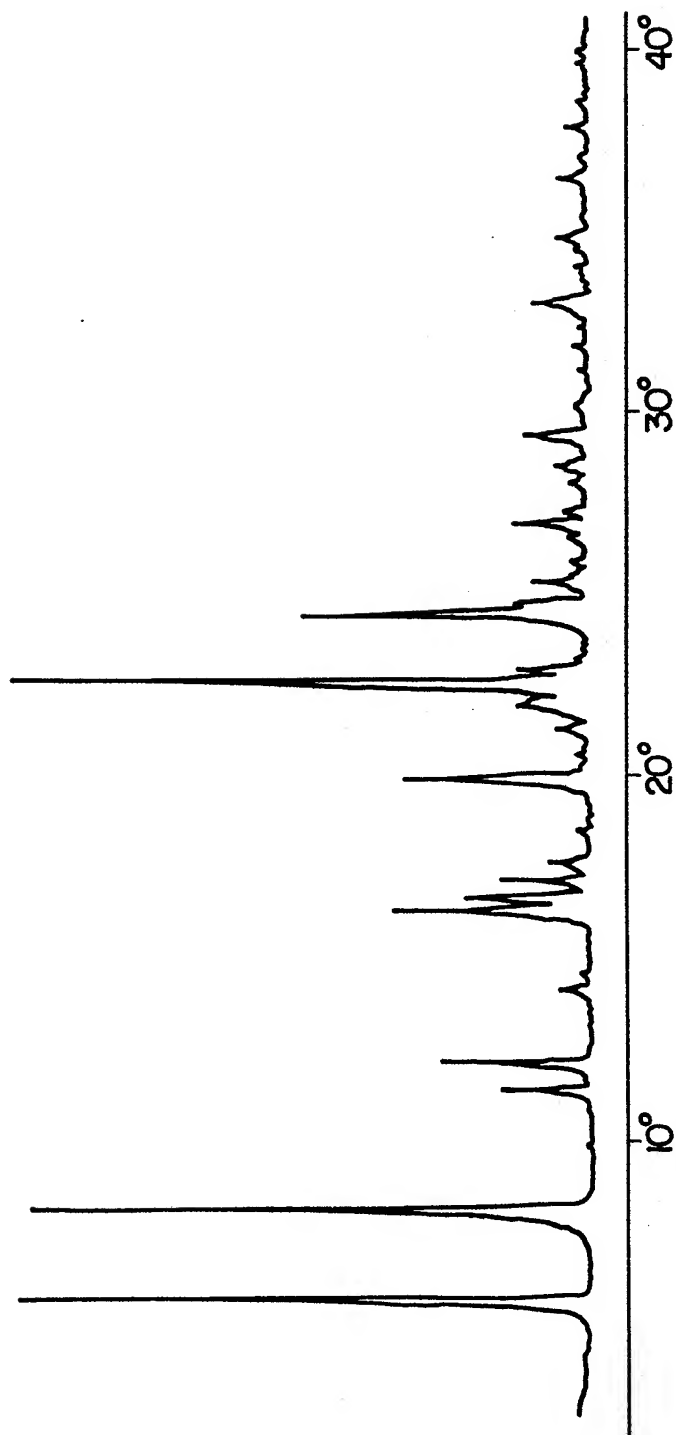


FIG. 3

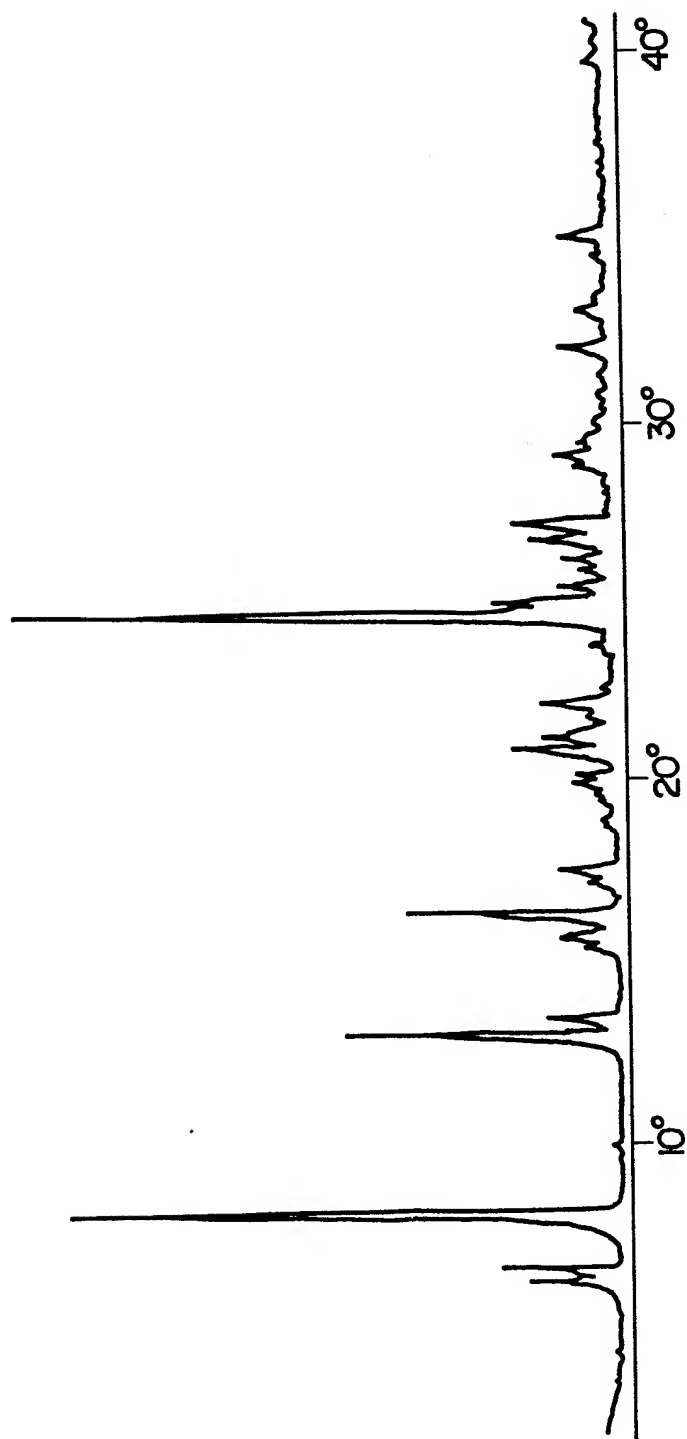


FIG. 4

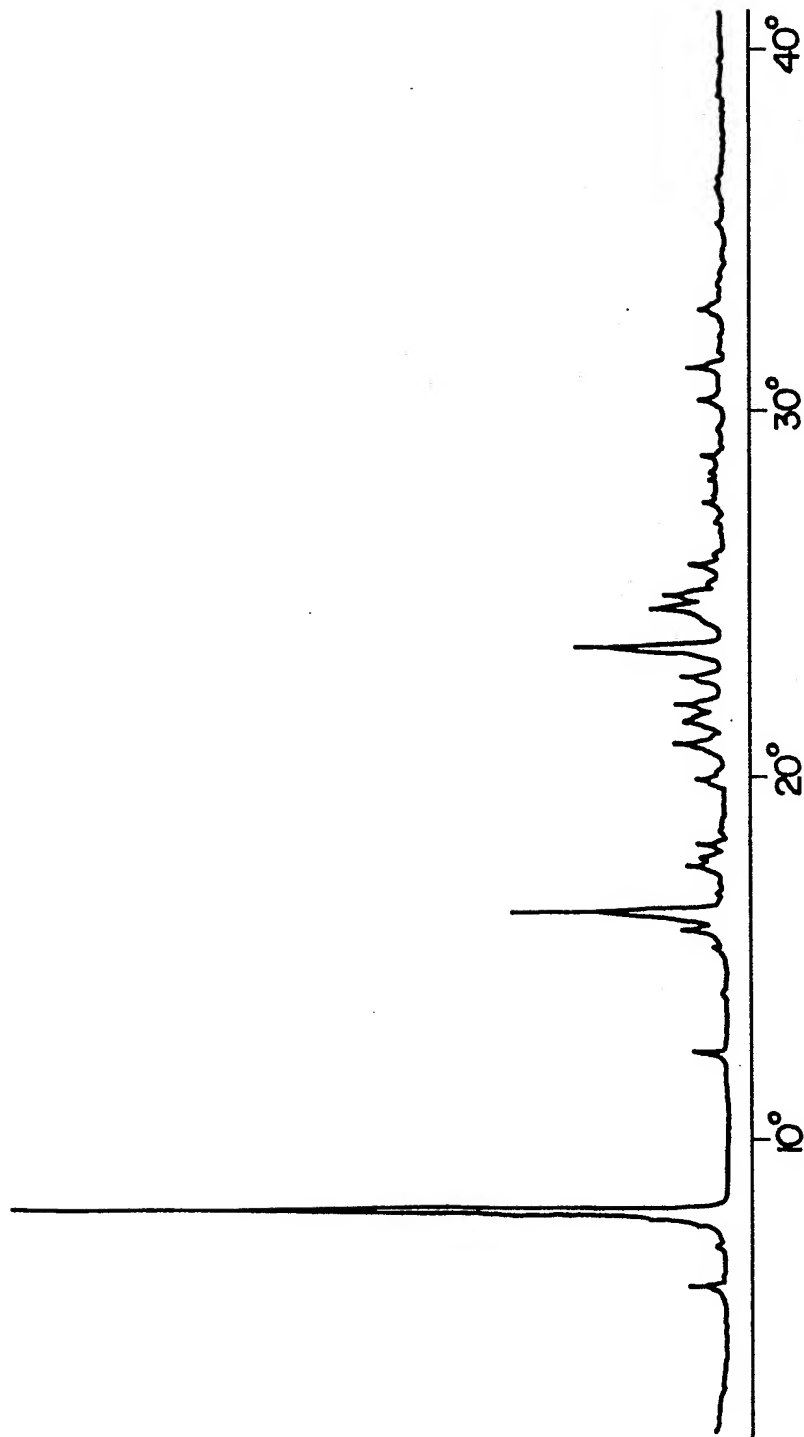
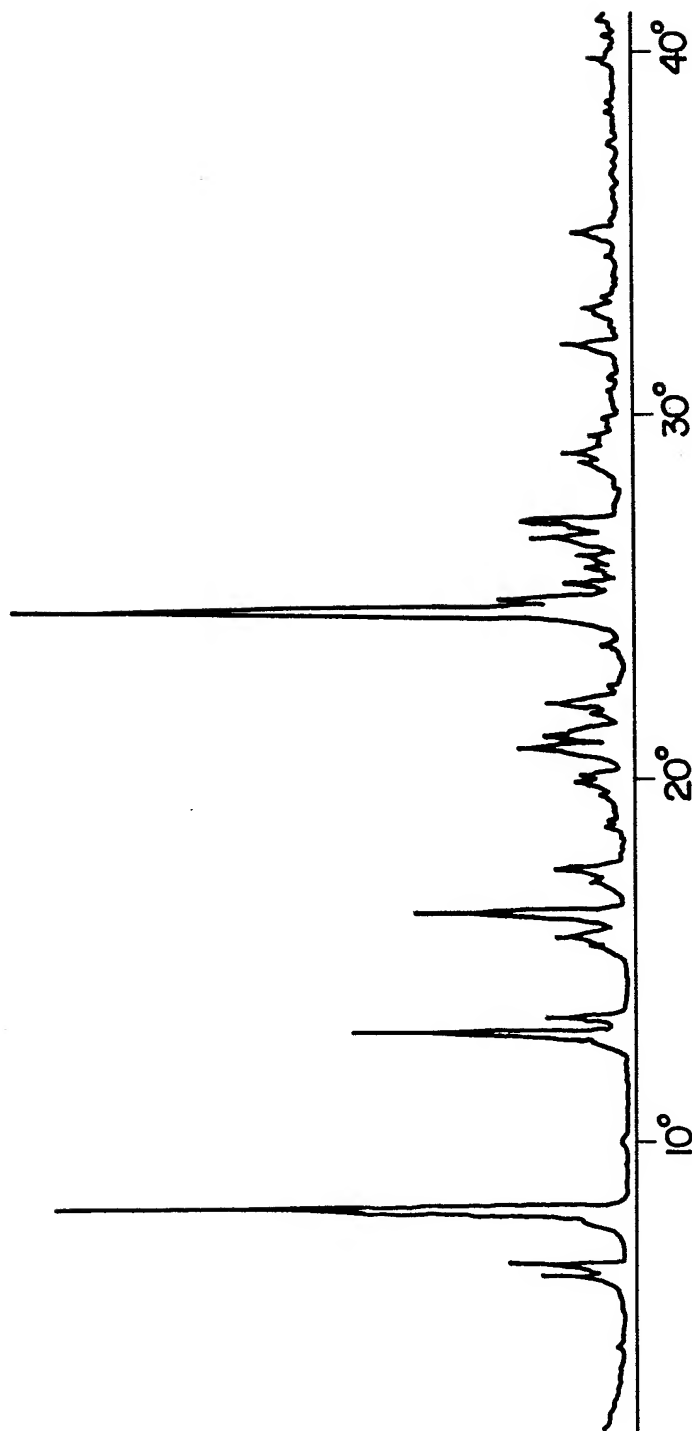


FIG. 5





European Patent
Office

EUROPEAN SEARCH REPORT

0107972

Application number

EP 83 30 6534

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
D, X	JAPANESE PATENTS GAZETTE (DERWENT), vol. W27, 12th August 1975, abstract no. 45194 & JP - A - 50 025 544 (SUMITOMO CHEM IND K.K.) 18-03-1975	1	C 07 C 57/58 C 07 C 51/487 C 07 B 19/00
A	--- JAPANESE PATENTS GAZETTE (DERWENT), vol. X06, 17th March 1976, page 4, abstract no. 10328 & JP - A - 50 126 635 (SUMITOMO CHEMICAL K.K.) 04-10-1975	1	
A	--- US-A-4 297 282 (OHASHI et al.) * Column 4, lines 48-60 * -----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 C 57/00 C 07 C 51/00 C 07 B 19/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 23-01-1984	Examiner KLAG M. J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	